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Overview

Those mysterious sequences of satellite DNAs

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INTRODUCTION

Since the early beginnings of understanding the genome structure, it has been realized that highly abundant, noncoding DNA sequences repeated in tandem, satellite DNAs, compose significant portions of every eukaryotic genome *(1, 2)*. Satellite DNAs are located in heterochromatic chromosomal regions usually formed around centromeres and at chromosome termini at interstitial positions. Little is known about functional significance of these sequences, although many reports support involvement of satellite DNAs in processes related to complex structural and functional features of eukaryotic chromosomes, particularly in centromeric and pericentromeric regions (Figure 1; for example, 3, 4, 5, 6 and references therein). In this regard, satellite sequences located within and around centromeres attract a considerable attention, and are the most explored fraction among satellite DNAs (reviewed in *6*).

The main feature of satellite DNAs is sequential arrangement of their repeating units, or satellite DNA monomers, which reiterate one after the other building arrays that can be several tens of Mb long (*1, 2, 3, 6*). Many satellite DNAs populate genomes, and they are usually unrelated in the nucleotide sequence, monomer length and complexity, as well as in evolutionary history. It can be reasoned that satellite DNAs show only two common features, tandem arrangement of monomer repeats and heterochromatin localization, while all other characteristics are apparently different. Extreme diversity of satellite DNAs raised major difficulties in deriving general conclusions, and many important questions remain open even after several decades of molecular genetic and cytogenetic studies done on this highly abundant genomic component. Recently, one new challenging field of research is opened by addressing transcription of satellite DNAs and its impact, particularly in relation to formation and maintenance of heterochromatin structure (*7*).

The particular limitation in satellite DNA research is posed by tandem repetitions and low variability of satellite monomers, what makes them hard to assemble and map into long contigs of genomic sequences. As a consequence, satellite repeats are underrepresented in outputs of genome projects and high-resolution view on sequential organization of DNA in heterochromatin remains obscure, apart from rare exceptions (*8, 9, 10*). The problem of accessibility of satellite DNAs to current sequencing and assembly techniques illustrates the finding that dominant satellite DNA of *Tribolium castaneum* (*11*) builds 17 % of the genome but in the assembled sequence it was represented with only 0.1% (*12*). The current strategy to study satellite DNAs therefore still relies on analyses of randomly cloned monomers and short multimers obtained after digestion of genomic DNA with appropriate restriction

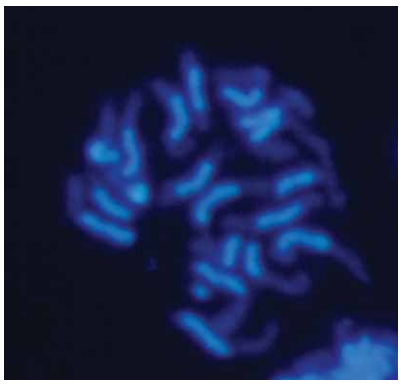

Figure 1. *DAPI-stained* Tenebrio molitor *chromosomes (2n=20). While large blocks of pericentromeric heterochromatin are easily observable, cytogenetic techniques could not detect interstitial and subtelomeric heterochromatin in this organism.*

endonucleases and their mapping by fluorescent *in situ* hybridization (FISH).

BEETLES, NEMATODES AND MOLLUSKS AS EXPERIMENTAL ORGANISMS IN SATELLITE DNA STUDIES

Extreme diversity of satellite DNA sequences and complexity of their possible functional roles urge for focusing on many different organisms, instead onto a limited number of established model species. The research on satellite DNAs at Ruđer Bošković Institute (Department of Molecular Biology) was initialized more than two decades ago, and since then species belonging to three invertebrate clades, tenebrionid beetles, root-knot nematodes and bivalve mollusks, proved to be of exceptional interest.

The genomes of tenebrionid beetles are characterized by massive blocks of pericentromeric heterochromatin, populated predominantly with one or two extremely abundant satellite DNAs distributed on all chromosomes of the complement (Figure 2) (*13, 14, 15*). Among beetles, *Tribollium castaneum* emerged as the second insect model organism after *Drosophila*, and its sequenced genome was recently published (*16*). Root-knot nematodes of the genus *Meloidogyne* are parthenogenetic plant-parasitic organisms with holocentric chromosomes and relatively low abundance of each satellite DNA (*17, 18, 19* and references therein). Among them, *Meloidogyne incognita* and *Meloidogyne hapla* genomes are available (*20, 21*), and others are anticipated in the near future. Constitutive heterochromatin in the bivalve mollusk species often shows low abundance (*22*), and, in some species, heterochromatin bands in pericentromeric regions could not be even detected (*23*). In accordance, genomes of studied mollusks comprise large number of satellite DNAs but amplified in a relatively low abundance, usually not exceeding 1% of the genome (*24, 25, 26*).

Some of achievements obtained by studying satellite DNAs in the above mentioned organisms deserve more detailed attention, because of their general impact on understanding satellite DNAs. The most important are, from my point of view, studies that established the model of evolution of satellite DNAs and helped to reconstruct the life-cycle satellite DNAs may have in general (*18, 27, 28, 29, 30, 31*), studies that characterized structural features of satellite sequences that may be under selective constraints (*11, 32, 33*; reviewed also in *34*) and the research that helped to understand unexpected organizational patterns of satellite repeats in some organisms (*31, 35, 36*). All these results together helped to build an integrated view on satellite DNAs and their evolution.

In order to summarize at least part of current views and contribution of the work done at the Department of Molecular Biology of Ruđer Bošković Institute, several aspects of satellite DNAs are selected to be discussed in this review. The first issue is about the coding potential of satellite DNAs, the second deals with the satellite DNA sequence evolution, while the third concerns organizational patterns of satellite DNA distribution.

CODING POTENTIAL OF SATELLITE DNAS

Functional potential incorporated in DNA sequence elements

Information is not necessarily contained in the whole monomeric unit of satellite DNA sequence; instead, short sequence segments within the monomer can act as motifs involved in putative functional interactions in the

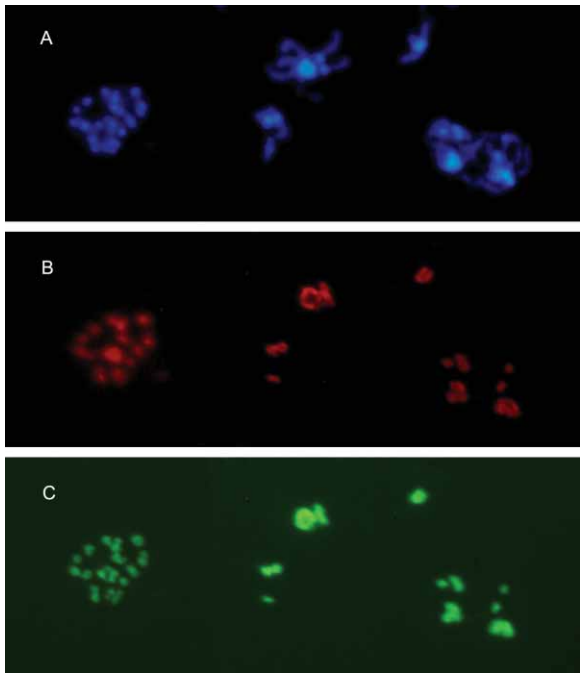

Figure 2. *Chromosomes of the beetle* Tribolium audax *(2n=20+ss) stained with DAPI (A), and hybridized with TRITC-labeled TAUD2 repeat (19% of the genome;* 31*) (B). The same plate hybridized with TAUD1 satellite DNA (40% of the genome;* 31*) labeled with the fluorochrome FITC (C). Left, mitotic metaphase chromosomes; right, chromosome bouquets at the first meiotic division.*

heterochromatin. It is assumed that for this reason, parts of monomer sequences or particular nucleotide positions evolve under different mutation rates (37, 38). The best known example is CENP-B box, the 17-bp-long sequence motif of human alpha satellite DNA (39, 40). CENP-B box is able to bind the CENP-B protein, which probably facilitates the kinetochore formation. Sequence motifs similar to the CENP-B box were found in satellite DNAs from various organisms, including *Tribolium* beetles, but their functionality was not evaluated (for example, *41, 42, 43*). Other oligonucleotide motifs of unknown function were anticipated in some unrelated satellites (*44*). Clustered satellite monomer variants containing DNA methylathion-sensitive sites as a functional motif represent sequence determinant that defines epigenetic modification and differentiates pericentrimeric heterochromatin from centrochromatin in *Arabidopsis thaliana* and maize (*45*).

Distribution of nucleotide divergences in monomers of a satellite DNA and/or among monomers of related satellites often show alternation of sequence segments rich in mutations with segments in which mutations are underrepresented. This uneven distribution of variability was observed in many satellites from different organisms, as diverse as human and *Arabidopsis* (*37, 38, 46*), tenebrionid beetles (*33, 47, 48*), root-knot nematodes (*18, 49*) and mollusks (*26, 30*). It is generally assumed that conserved sequence segments represent potentially important yet uncharacterized motifs involved in functional interactions, or regions of increased similarity may be needed as sites that promote homologous recombination (*46, 50, 51*). In the same time, variable segments may be of functional significance as well, for example as spacers ensuring proper periodicity of sequence motifs (*46*) or in interactions with rapidly evolving proteins of centromeric chromatin (*52*). Accordingly, the most polymorphic sites in the satellite DNA variants shared between the beetle *Palorus subdepressus* and several other distant beetle species are in the same time those with ancestral mutations (*47*).

Structural features of satellite DNAs

Secondary and tertiary structures of the DNA molecule (dyad structures and sequence-induced bent helix axis) can be induced by particular distribution of nucleotides. Different combinations of nucleotides can produce similar effects, thus establishing structure as a common feature. Dyads formed by inversely duplicated sequence segments exist in monomers of many satellite DNAs and are assumed to be associated with heterochromatin condensation and/or with centromeric function (*53, 54*). In this regard, short inverted segments in the vicinity of about 20–40 nucleotides long nearly homogeneous A+T tracts were detected in monomers of *Tribolium confusum* (*55*) and *Tribolium castaneum* (peri)centromeric satellites (*11*).

While short inverted sequence segments can be often detected in satellite monomers, those based on inverse duplications of whole repetitive (sub)units are less frequent. The most remarkable detected inverted repeats are found in satellites from *Tribolium* species. These satellites are characterized by complex monomers that can be over one kilobase long, and are composed of inversely oriented subunits capable of forming large dyad structures (*29, 31, 43, 56*). In this context, it was suggested that structural properties of the two repetitive elements and similarities in sequence dynamics resulted in parallel evolution of these sequences and formation of equivalent heterochromatin architecture in the two sibling species *Tribolium madens* and *Tribolium audax* (*31*).

Inversely oriented sequence elements may be recognized by mechanisms related to transposition which can contribute to dispersal of such sequence segments. Sequence similarities indicate evolutionary relations between some satellite DNAs and mobile elements or their segments (*57, 58* and references therein). For example, the family of satellite DNAs broadly distributed among mollusk species, assumed to originate over 500 Myr ago, shares sequence similarity with a putative miniature inverted-repeat transposable element (MITE) detected in oyster (*30*). It can be speculated that transposition-related processes might have a dominant role in building DNA components of heterochromatin in these organisms.

The sequence-induced bent helix axis is a consequence of periodic distribution of nucleotides, in particular of short tracts of As and/or Ts phased with a turn of double helix. This feature is prominent in many satellite DNAs (*59, 60*), and is thought to facilitate the tight packing of DNA in heterochromatin (*61*) (Figure 3). In tenebrionid beetles, the curved helix axis of *Tenebrio molitor* satellite DNA can form left-handed superhelical structure that might be involved in specific positioning of the satellite DNA around nucleosomes (*32*). Structures similar in geometry can be also formed by several satellites from species of the related genus *Palorus* (*62, 63*). Although unrelated in the nucleotide sequence, in addition to the similar tertiary structure these satellites share nearly identical monomer length of about 140–145 bp.

Monomer length can be an additional feature of satellite DNAs that evolves under constraints. Monomers of many satellite DNAs can be grouped in the size-range of 140–180 bp and 300–360 bp, what is assumed to be

Figure 3. *Three-dimensional models of bent DNA helix axis of monomers and tetramers of* Tribolium anaphe *(TANAPH) and* Tribolium destructor *(TDEST) satellite DNAs. Although similar in the monomer length, the predicted tertiary structure of these satellites differs significantly. However, satellites share non-random distribution of sequence variability, CENP-B box-like motifs and ability to form dyad structures (*33*).*

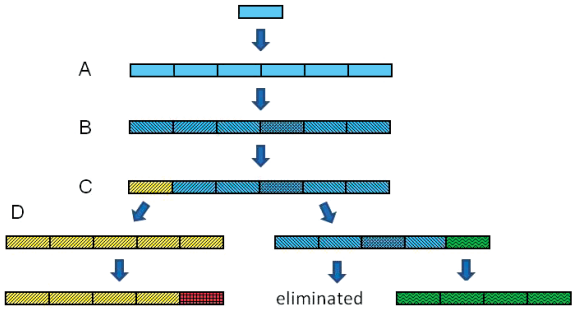

Figure 4. *The two phases in satellite DNA evolution and diversification of satellite DNA sequences. In the first phase, satellite DNA is formed by tandem amplification of a DNA sequence (A). Following amplification, sequence variability profile of monomer variants is formed, and because of specificities of concerted evolution it can remain stable for long time-periods (phase two, B). However, mutations accumulate in peripheral monomers (C), which can be amplified in a new satellite DNA, and the process repeats itself (D). Copy number of monomers changes significantly during the satellite DNA lifespan (not shown), what can eventually lead to extinction of some satellite DNAs. While selection of long-living satellite DNAs is thought to be driven by functional constraints, expansions and contractions of satellite repeats is a random process* (18).

linked with the length of a DNA wrapped around one or two nucleosomes (*2, 5*). While bent DNA and strict monomer length are characteristic for satellites of the studied *Tenebrio/Palorus* beetles, prominent segments capable of forming dyad structures, can be observed in *Tribolium* satellites discussed above. However, these features are not always mutually exclusive and inversely repeated segments flanked by a stretch of A+T rich sequence were found in *P. subdepressus* satellite (*62*).

SPECIFICITIES OF SATELLITE DNA EVOLUTION

Concerted evolution

High sequence homogeneity (usually > 95%) within a family of satellite DNA monomers is a consequence of their non-independent evolution, a phenomenon called concerted evolution. It is achieved in a two-level process known as molecular drive, in which mutations are homogenized (either spread or eliminated) among members of a repetitive family in a genome, and concomitantly fixed within a group of reproductively linked organisms (*64, 65*). Level of sequence variability in a satellite DNA is therefore equilibrium between the process of accumulation of mutations and the rate of their spread (or elimination) among satellite monomers. Sequence homogenization is a consequence of molecular mechanisms of nonreciprocal exchange, such as unequal crossover and gene conversion, reinsertion of segments amplified by extrachromosomal circular DNA, and mechanisms related to transposition (*58, 65, 66, 67, 68*). On the contrary, fixation of monomer variants is driven by meiosis and chromosome segregation (*65, 69, 70*). The outcome of this process is higher homogeneity of satellite monomers within than between bisexual taxa. Mutations in a satellite DNA family accumulate in gradual manner (*71*), and depending on the rate of accumulation and spread they can be phylogenetically informative, for example, on the species level (*72*), on the level of ecotype-specific variants (*46*) or on the level of phylogeographic clades (*73*). In unisexual organisms, fixation is disabled due to parthenogenetic reproduction, and sequence variability of satellite monomers is comparable among all organisms, regardless their taxonomic position within the group of species (*69, 70*).

Long-time conserved satellite DNA sequences

Appearance, spread and assimilation of mutations in course of sequence homogenization of satellite monomers is essentially stochastic process which is assumed to result in rapid accumulation of divergences in satellite sequences of reproductively isolated organisms (*74, 65*). However, monomer sequences of some satellite DNAs could not be discriminated even when detected in species separated for periods of tens of millions years (for example, *28, 73, 75, 76*). The most extreme example described until now is the mollusk BIV160 satellite family, estimated to exist for over 500 million years (*30*). The basis for extreme conservation of satellite sequences is poorly understood. One assumption is that mechanisms of molecular drive favor some particular subsets of monomer variants (*74, 77, 78*). Conservation can be also a consequence of constraints imposed on satellite sequences, and/or it can be a result of slowed down mutation and homogenization rates (*30, 73, 76, 78, 79*).

Even if a satellite DNA sequence is conserved during long evolutionary periods, new satellite repeats can be formed by amplification of mutated monomers nascent at array borders (*29*), where mutations rapidly accumulate because of reduced efficacy of homogenization mechanisms (*67, 80, 81*). In this way, satellite DNAs represent a unique sequence type that unifies two features in the same time, sequence stability over long DNA segments and during long periods of time, and the potential to produce altered variants that can be amplified as a new satellite sequence (*6, 30*). This dualism may be particularly important in centromeric regions, where interactions between DNA and centromeric histone-like protein CenH3 must remain stable, and, to achieve this stability, the DNA sequence must have potential to coevolve with the rapidly changing protein component (*82*).

Copy number alterations and the library model

Despite the fact that at least some satellite DNA sequences can remain unaltered during long evolutionary periods, satellite DNAs are among the most rapidly evolving genome components, differing even among closely related species in the composition, copy number, and/or nucleotide sequence (*6*). The most rapid changes are copy number alterations of satellite monomers, assumed to be mostly the consequence of unequal crossover (*83*).

Since more than one satellite DNA resides in a genome, copy number fluctuations represent extremely efficient mechanism capable to change satellite DNA content in heterochromatin by expanding and suppressing already existing satellite sequences. The model assuming existence of a collection or a library of satellite DNAs shared by a group of related species was originally suggested by Fry and Salser (*84*) but its existence was for the first time experimentally proved 21 years later, by studying distribution of satellite repeats in the genus *Palorus* (*27*) (see also Figure 3 in 6). Since then, satellite DNAs shared among species in different abundances were detected in various taxa (*49, 85, 86, 87*). The concept of copy number alterations in satellite DNA libraries can be extended on monomer variants of a single satellite DNA (88). It can be therefore assumed that satellite DNA libraries represent a widespread mode of satellite DNA organization in heterochromatin (*6*) (Figure 5 in 30).

Sequence comparisons of related satellite DNAs in root-nematode species indicated two phases in evolution of satellites in the library (*18*). The first phase is tandem amplification of a sequence and formation of a new satellite DNA, and in the second phase satellite DNA sequences can continue persisting for long evolutionary periods, as discussed above (Figure 4). While it can be assumed that selection of a sequence capable to build a new long-living satellite DNA is driven by functional constraints, appearance and disappearance of satellite families in the library is essentially stochastic process (*18*). These events are congruent with evolutionary history of species, and presence or absence of satellite DNAs can be used as a reliable character in phylogenetic studies (*19*).

Dynamics of satellite DNA content and composition can affect genome functions and evolution by itself. Rapid expansions and contractions of satellite DNA arrays in centromeric regions can cause incompatibilities in protein-DNA interactions in centromeres of hybrid organisms, and raise a barrier that will ultimately lead to reproductive isolation and speciation (*5, 27, 89*). Alterations in copy numbers of satellite DNA sequences can be associated with chromosome instability and genome reorganization that will also lead to speciation (*90*). Genome restructuring by chromatin diminution in somatic cells during development of some organisms is associated with rapid changes in satellite DNA content (*91*).

ORGANIZATIONAL PATTERNS OF SATELLITE DNA MONOMERS

Within arrays of tandem repeats, variants of satellite DNA monomers are often grouped into chromosome-specific subfamilies distinctive by diagnostic mutations. This pattern is typical, for example, for human α-satellite (*92, 93*). It is reasoned that diversification of satellite monomers into subfamilies is a consequence of more efficient homogenization between proximal than between distal monomer variants (*83, 65, 67*). Dissimilar organizational pattern is found in *Tenebrio molitor* and some other tenebrionid beetles, in which satellites are distributed in pericentromeric heterochromatin of all chromosomes, without forming chromosome-specific subfamilies of monomers (*13, 35, 36, 94*). In addition, two satellites coexisting in genomes of the two sibling species *Tribolium madens* and *Tribolium audax* form short intermingling arrays, again, uniformly distributed on all chromosomes (*31, 36*). Comparably, expansions and contractions of non-homologous satellites within a library do not alter their co-localization in pericentromeric heterochromatin of all chromosomes even if contribution of each family is changed from < 0.5% to >30 % (*27, 28*).

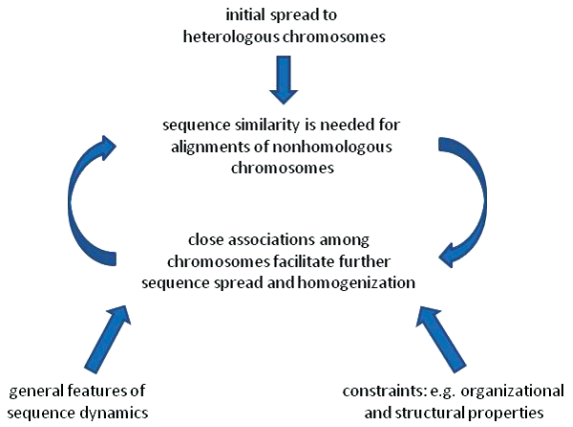

Figure 5. *The proposed synergy between the bouquet stage and satellite DNA sequence dynamics is assumed to facilitate uniform distribution of satellite DNAs on all chromosomes of tenebrionid beetles.*

Uniform distribution of satellite DNAs and their monomers variants on all chromosomes of the complement seems to be an organizational specificity of tenebrionid beetles. A stage facilitating uniform distribution of satellite DNAs in beetles could be meiotic bouquets, observed in almost all species studied until now *(31, 36)* (Figure 2). In the first meiotic division, all chromosomes align together with their pericentromeric regions, in which given satellites represent dominant DNA substrate. This opportunity can give a chance for recombination and spread of satellite DNA sequences. It can be proposed that sequence similarity in pericentromeric heterochromatin facilitates alignments of heterologous chromosomes, while in turn, alignment itself is required for efficient dispersal of satellite DNAs on all chromosomes (Figure 5). Mechanisms of illegitimate recombination were invoked to explain genesis of similar highly interspersed pattern of two satellites distributed on microchromosomes of *Drosophila* species (*51*). These recent results oppose the traditional idea about heterochromatin as recombinationally inert genome compartment, and indicate high level of recombination events in heterochromatin of at least some species (*31, 51*).

A CONCLUDING REMARK

Many things have changed during the period of over two decades, since the research on satellite DNAs at Ruđer Bošković Institute was initialized. At the beginning, the majority of scientific community disregarded

satellite DNAs as an odd genomic component, without much use either for the genome or for the knowledge about the genome, simply because they do not harbor genes. However, in the genomic era, it became evident that these sequences are important and that exploring heterochromatin is indispensable to fully understand the eukaryotic genome (*95*). Although satellite DNA sequences are still far from being fully understood, functional potential that they have in maintaining higher--level organizational and functional traits of every eukaryotic genome is attracting more and more attention, and years to come will certainly bring new ideas and concepts that will help to demystify these unusual genomic components.

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